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Ab Initio Calculation of Vibrational Circular Dichroism Spectra of Chiral Natural Products Using MP2 Force Fields: Camphor

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Vibrational circular dichroism (VCD) spectroscopy[1] is potentially a powerful tool for elucidating the stereochemistry—including the absolute configuration—of chiral molecules. Its widespread application in practice requires a reliable methodology for the prediction of VCD spectra. *Inter alia,* a harmonic force field of adequate accuracy is a *sine qua non.*

Harmonic force fields are most accurately calculated using *ab initio* methods.[2] Practicability is greatest and accuracy is least at the lowest, SCF level of approximation. SCF frequencies differ from experimental frequencies by 10–15%.[2,3] VCD spectra calculated using SCF force fields generally differ substantially from experimental spectra (with the exception of very small, symmetrical molecules).[4-6] Better-than-SCF force fields are thus essential for the reliable prediction of VCD spectra. Correlation is most efficiently included when the MP2 methodology is used.[3] MP2 frequencies differ from experimental frequencies by only ~5% at medium basis set levels[3] and are even more accurate at large basis set levels.[7] MP2 force fields should thus provide substantially improved predictions of VCD spectra. This expectation is supported by calculations for very small chiral molecules.[6,8] However, until very recently, calculations of MP2 force fields have been impracticable for much larger molecules.

The recent introduction of semidirect techniques[9] has dramatically increased the practicability of analytical derivative calculations of MP2 harmonic force fields.[10] As a result, calculations of VCD spectra based on MP2 force fields are now possible for much larger molecules than heretofore. This in turn considerably enlarges the range of potential applications of VCD spectroscopy. In this Communication, we demonstrate that the practicability of calculations of VCD spectra based on medium basis set MP2 force fields now extends to chiral natural product molecules. Specifically, we report the calculation of the VCD spectrum of the monoterpene camphor (1,7,7-trimethylbicyclo[2.2.1]heptan-2-one, **1**) utilizing a 6-31G* MP2 force field. Comparison to the experimental VCD spectrum of **1** further documents the accuracy of VCD spectra predicted using medium basis set MP2 force fields.

Prediction of the absorption and VCD spectra of **1** at the harmonic level of approximation requires the calculation of the harmonic force field, atomic polar tensors (APTs), and atomic axial tensors (AATs) at the equilibrium geometry.[11] In this work, the harmonic force field and APTs of **1** have been calculated at the frozen-core MP2 (FC-MP2) level of approximation[12] and at the 6-31G* basis set level[3] (197 basis functions) using semidirect analytical derivative techniques via a CRAY-YMP implementation of GAUSSIAN 92.[13] AATs have been calculated using the Distributed Origin gauge,[14] in which

$$(\mathbf{M}^{\lambda}_{\alpha\beta})^{\mathrm{O}} = (\mathbf{I}^{\lambda}_{\alpha\beta})^{\vec{R}^{\mathrm{o}}}_{\lambda} + \frac{i}{4\hbar c}\sum_{\gamma\delta}\epsilon_{\beta\gamma\delta}R^{\mathrm{o}}_{\lambda\gamma}\mathbf{P}^{\lambda}_{\alpha\delta}$$

where $(\mathbf{M}^{\lambda}_{\alpha\beta})^{\mathrm{O}}$ is the AAT of nucleus λ with respect to the molecular origin O, $(\mathbf{I}^{\lambda}_{\alpha\beta})^{\vec{R}^{\mathrm{o}}}_{\lambda}$ is the electronic AAT of nucleus λ calculated with the origin at the equilibrium position of nucleus λ, $\vec{R}^{\mathrm{o}}_{\lambda}$, and $\mathbf{P}^{\lambda}_{\alpha\beta}$ is the APT of nucleus λ. In this work, the "local" AATs, $(\mathbf{I}^{\lambda}_{\alpha\beta})^{\vec{R}^{\mathrm{o}}}_{\lambda}$, are calculated at the SCF level of approximation and at the 6-31G* basis set level using analytical derivative techniques[15] via a CRAY-YMP implementation of CADPAC 5.0.[16] As stated above, the APTs are calculated at the FC-MP2 level of approximation. The resulting "semi-MP2" AATs thus include correlation but less completely than the MP2 APTs.

Calculated vibrational frequencies, dipole strengths, rotational strengths, and anisotropy ratios are listed in Table 1. Experimental measurements of the VCD of **1** have been reported for the C—H stretching,[17] C=O stretching,[18] and mid-IR (>900 cm^{-1})[19] spectral regions. The mid-IR VCD of (1*R*,4*R*)-(+)-**1** is reproduced in Figure 1, together with the corresponding unpolarized absorption spectrum. Experimental frequencies, dipole strengths, and rotational strengths have not been reported. We have therefore synthesized absorption and VCD spectra from the calculated values using Lorentzian band shapes.[20] The resulting spectra are compared to experiment in Figure 1.

Allowing for the overestimation of vibrational frequencies expected of MP2 force fields,[3] predicted absorption and VCD spectra are in obvious correspondence with the experimental C=O stretching and mid-IR spectra and permit their straightforward assignment, as detailed in Table 1 and Figure 1. All fundamental excitations of **1** in the range 900–2000 cm^{-1} can be unambiguously assigned unless (a) they are unresolved from adjacent transitions

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Table 1. Calculated and Experimental Frequencies, Dipole Strengths, Rotational Strengths, and Anisotropy Ratios of **1**[a]

calculation				experiment	
$\bar{\nu}$[b]	D	R	g	$\bar{\nu}$[c]	g[d]
1807	294.6	12.3	0.2	1745	0.2
1587	14.7	−2.9	−0.8	1481	
1576	15.4	11.4	3.0	1470	2.1
1570	1.7	1.6	3.9		
1561	6.3	−0.8	−0.5		
1556	11.0	6.0	2.2		(+)
1551	14.2	4.0	1.1	1453	(+)
1547	21.5	−1.5	−0.3	1449	(−)
1542	8.4	−1.1	−0.5		(−)
1521	27.6	−2.3	−0.3	1417	−0.6
1475	28.2	−5.5	−0.8	1391	−0.9
1459	15.3	2.8	0.7	1377	(+)
1454	22.7	−1.7	−0.3	1371	(−)
1395	25.3	10.7	1.7	1323	1.7
1367	8.8	−4.8	−2.2	1299	(−)
1364	2.5	−5.0	−8.0	1295	(−)
1341	24.7	−0.2	0.0	1277	0.5
1312	7.7	14.3	7.4	1245	8.9
1299	2.3	1.3	2.2		
1286	3.0	2.4	3.2	1220	
1259	8.0	−4.5	−2.2	1198	(−)
1255	2.7	−3.0	−4.5	1192	(−)
1223	9.2	6.8	3.0	1166	5.6
1214	4.3	−6.7	−6.3	1154	−5.8
1188	5.6	5.0	3.5	1128	3.1
1147	14.2	−3.9	−1.1	1094	−0.6
1124	9.5	−6.9	−2.9	1079	
1094	112.7	−16.7	−0.6	1045	−2.5
1069	21.2	−6.2	−1.2	1021	−1.3
1061	12.2	6.1	2.0	1012	2.2
1037	1.6	−1.2	−2.9	986	−4.6
999	12.5	−4.6	−1.5	950	(−)
989	1.4	−5.2	−15.1		(−)
983	11.4	7.6	2.7	936	(+)
970	6.0	15.3	10.1	925	10.7
955	2.9	−12.8	−17.8	913	−12.5

[a] Frequencies, $\bar{\nu}$, in cm^{-1}; dipole strengths, D, in 10^{-40} esu^2 cm^2; rotational strengths, R, in 10^{-44} esu^2 cm^2; anisotropy ratios, g, dimensionless and in 10^{-4}. Rotational strengths and anisotropy ratios are for the (1*R*,4*R*)-(+) enantiomer of **1**. [b] Fundamentals of **1** are numbered in ascending order; the 955–1807-cm^{-1} modes listed are fundamentals 24–59. [c] Peak frequencies from a 1-cm^{-1} resolution spectrum of (+)-**1**, 0.45 M in CCl_4, measured in these laboratories. Over the range 1575–900 cm^{-1}, our spectrum is qualitatively identical to that in Figure 1. [d] Estimates from Figure 10 of ref 19, except for band 59, which is from ref 18. Only signs are given in the case of overlapping bands whose anisotropy ratios cannot be obtained without deconvolution.

or (b) their absorption and VCD intensities are both too weak to be observed.

The agreement of calculated and experimental absorption and VCD spectra is substantially worse in the C—H stretching region, and a detailed assignment is not possible. This is attributable to the large number (16) of closely spaced C–H stretching transitions and, in addition, to the inevitable incursion of Fermi resonance.

The overall agreement of predicted and experimental mid-IR VCD intensities is qualitatively excellent. In only one case is the sign of the calculated VCD opposite to that observed. For this case, fundamental 43, both calculated and observed VCD intensities are very weak. The absolute configuration of **1**[21] is unambiguously confirmed.

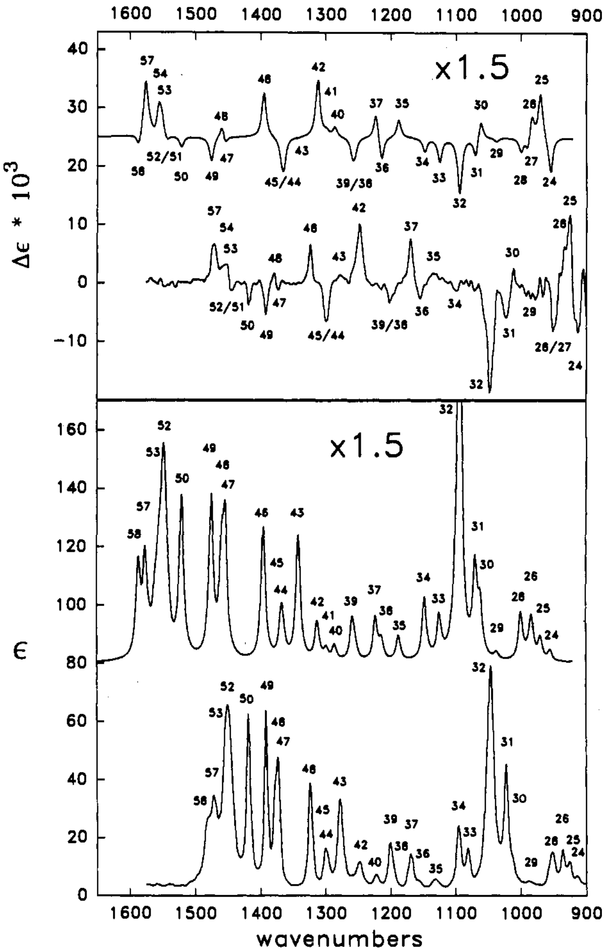

Figure 1. Experimental (0.60 M in CCl_4; ref 19, with permission) and calculated mid-IR absorption and VCD spectra of **1**. VCD spectra are for (1*R*,4*R*)-(+)-**1**. Calculated spectra use Lorentzian band shapes; the bandwidth parameter, γ, is arbitrarily chosen to be 4.0 cm^{-1} for all bands.

Although experimental rotational strengths have not been reported, anisotropy ratios for resolved transitions can be estimated from the experimental absorption and VCD spectra. Values obtained are compared to the calculated values in Table 1. The quantitative agreement is of the level expected from calculations on smaller molecules.[6,8]

We have shown that the prediction of the VCD spectra of chiral molecules comparable in size to **1** using medium basis set MP2 harmonic force fields is now practicable and can be expected to be of excellent qualitative accuracy. This development considerably expands the range of application of VCD spectroscopy.

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